Trial Statistical Analysis Plan

c09133040-02

BI Trial No.:	1199.224
Title:	An open label Phase I of oral nintedanib plus weekly docetaxel therapy in patients with locally advanced or metastatic lung adenocarcinoma after failure of platinum-based first line chemotherapy
Investigational Product(s):	Nintedanib, BIBF 1120
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	21 FEB 2017 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
AESI	Adverse Event of Special Interest
ATC	Anatomical, Therapeutic, Chemical
BI	Boehringer Ingelheim
BSA	Body Surface Area
CR	Complete Response
CT	Concomitant Therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBLM	Database Lock Meeting
DLT	Dose Limiting Toxicity
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
EoT	End-of-Text
ICH	International Conference on Harmonisation
IPV	Important Protocol Violation
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
OR	Objective Response
PFS	Progression-free survival
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PR	Partial Response
PT	Preferred Term
PV	Protocol Violation
RECIST	Response Evaluation Criteria In Solid Tumours
RPM	Report Planning Meeting
SAE	Serious Adverse Event

Term	Definition / description
SD	Stable Disease
StD	Standard Deviation
SOC	System Organ Class
TCM	Trial Clinical Monitor
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO DD	World Health Organisation - Drug Dictionary

3. INTRODUCTION

As per International Conference on Harmonisation (ICH) E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP, c03239885-01), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, and randomization. This TSAP follows the Boehringer Ingelheim (BI) internal reference (1).

In the following, study medication always refers to nintedanib and docetaxel.

SAS® Version 9.4 (or higher) will be used for all analyses if not stated otherwise.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Although CTP Section 5.1.3.2 states that objective response will be confirmed by imaging after 4 weeks or later after the first occurrence of the response, the further endpoints Objective Response and Duration of Objective Response will be displayed in terms of unconfirmed response, as defined in Section 5.3 of this TSAP.

Otherwise, all analysis will be performed as planned in the CTP.

5. ENDPOINTS

All endpoints are defined in CTP Section 5.

5.1 PRIMARY ENDPOINTS

The primary objective of this trial is to determine the safety and tolerability of nintedanib in combination with weekly docetaxel by defining the Maximum Tolerated Dose (MTD) and recommending the dose for further trials in the development of this combination. Dose Limiting Toxicity (DLT) as assessed by the investigator and occurring during the first treatment cycle (first 28 days after start of trial medication) is the primary endpoint and will be used to determine dose escalation and the MTD. Definition of DLT is specified in CTP Section 5.3.6.

The MTD is defined as the highest dose combination studied for which the incidence of DLTs is no more than one out of six patients with a DLT during the first treatment cycle. In case escalation reaches dose level 3 (200 mg bid nintedanib given without interruption on days of docetaxel infusion) and no more than 1 out of 6 patients in experiences a DLT during the first 28-day cycle at this dose level, dose level 3 will be considered as the MTD.

Patients who were replaced during the first treatment cycle will not be considered for MTD determination. Those patients that have completed the first treatment cycle without having been replaced will be referred to as patients evaluable for MTD.

5.2 SECONDARY ENDPOINTS

There are no formal secondary endpoints defined in the CTP.

5.2.1 Key secondary endpoints

Not applicable, as no key secondary endpoints have been specified in the CTP.

5.2.2 Other Secondary endpoints

Not applicable, as no secondary endpoints have been specified in the CTP.

5.3 FURTHER ENDPOINTS

Further endpoints as specified in CTP Section 5.1.3 are:

- The pharmacokinetics ($C_{pre,ss}$) of nintedanib and its two metabolites (BIBF 1202 and BIBF 1202 glucuronide) for dose level 3 (nintedanib 200 mg bid in combination with docetaxel)

- Objective Response (OR), defined as best Overall Response of Complete Response (CR) or Partial Response (PR), where best Overall Response is determined according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 recorded from the date of first treatment administration until the earliest of disease progression, death, or last adequate tumour assessment before new anti-cancer therapy.

- Duration of OR, defined as the time from first documented CR or PR until the earliest of disease progression or death among patients with objective response.

- Progression free survival (PFS), defined as the time from first treatment administration until tumour progression or death from any cause, whichever occurs earlier.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

In this Phase I trial treatments are not randomized. Different dose levels of nintedanib in combination with weekly docetaxel will arise. The data will be presented for all cohorts separately and in total. To justify the MTD determination, DLTs occurring during the first treatment cycle will be presented separately from those occurring during the complete on-treatment period.

For the on-treatment period, the initial trial medication assigned at the beginning of the first treatment cycle will be used as label of the analysing treatment. Tables for the on-treatment period will contain a "total" column, representing all doses of trial medication combined.

The first treatment cycle starts with the first administration of any trial medication and lasts for 28 days.

Adverse Events (AEs) that have onset date during the Screening or Follow-Up periods will be displayed in separate listings from those occurred during the on-treatment period. Listings of AEs will not present a "total" category.

Labels of each analysing treatment period, analysis numbers, the labels used for display in the tables and listings in the CTR, as well as codes, decodes, sort order and labels for each trial medication used in this trial are provided in the technical document "ADS Plan".

6.2 IMPORTANT PROTOCOL VIOLATIONS

In this Phase I trial no per protocol population is defined. However, Important Protocol Violations (IPVs) should be identified for patients in the treated set.

Data discrepancies and deviations from the CTP will be identified for all treated patients. Listings of protocol deviations and of unresolved discrepancies will be provided to be discussed at the medical quality review meetings (MQRMs), e.g. deviations in drug administration, in blood sampling etc. At these meetings, it will be decided whether the discrepant data can be used as they are or whether the data have to be corrected in the clinical database.

Each protocol deviation must be assessed to determine whether it is an important protocol violation. A protocol violation (PV) is important if it affects the rights or safety of the study patients or if it can potentially influence the primary outcome measure(s) for the respective patients in a way that is neither negligible nor in accordance with the study objectives. PVs that do not influence the patient's rights and safety or the evaluability of the patients for the main study objectives are called non-important PVs. These are only considered when checking the trial quality in general.

If any manual IPVs are identified, they are to be summarised into categories and will be captured in the MQRM/RPM minutes via an accompanying Excel spreadsheet (2). The following table (Table 6.2: 1) contains the categories which are considered to be possible IPVs in this trial.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1[1]	Inclusion criteria not met	Inclusion criteria 1-5 not met as specified in the protocol.	None
	A2[1]	Exclusion criteria met	Exclusion criteria met as specified in the protocol	None
B		**Informed consent**		
	B1[1]	Informed consent not available/not done	Informed consent date missing	None
	B2[1]	Informed consent too late	Informed consent date was after Screening	None
C		**Trial medication and randomisation**		
	C1[2]	Incorrect dose taken	Medication kit assigned not matching treatment patient was assigned to	None
	C2[2]	Non-compliance	Patient missed more than 14 doses of nintedanib in one cycle, except for interruption due to AE	None
D		**Concomitant medication**		
	D1[2]	Prohibited medication use	Use of medication during the on-treatment period that is not allowed according to CTP	None
E		**Missing data**		
	E1[2]	DLT not recorded	AE that fulfils definition of a DLT is not indicated as DLT in the CRF	None

[1] IPV will be derived automatically
[2] IPV will be identified via individual review at MQRM/RPM/DBLM

6.3 PATIENT SETS ANALYSED

Screened Set:
This patient set includes all patients who have signed the informed consent. The screened set will be used for patient disposition tables.

Treated Set (TS):
This patient set includes all patients who were documented to have received at least one dose of study medication. The TS will be used for all safety and efficacy analyses.

MTD Evaluation Set:
This patient set includes all patients who were documented to have received at least one dose of study medication and were not replaced for the MTD determination. The MTD evaluation set will be used for the primary analysis of DLTs and MTD determination.

Rules for replacement are defined in CTP Section 3.3.4.3. The list of replaced patients will be provided by the Trial Clinical Monitor (TCM) no later than the last report planning meeting (RPM).

Pharmacokinetic Set (PKS):
This patient set includes all patients who received at least one dose of study medication at dose level 3 (200 mg bid nintedanib without interruption on days of docetaxel infusion) and that provide at least one observation for the pharmacokinetic (PK) endpoint value if they are not flagged for exclusion due to PK non-evaluability or an IPV relevant to the evaluation of PK endpoints, which will be decided no later than in the DBL meeting. It is used for the analysis of PK parameters.

Table 6.3: 1 Patient sets analysed

	Patient set			
Class of endpoint	TS	SCS	MTD evaluation set	PKS
Primary and key secondary endpoints	X		Primary analysis	
(other) Secondary and further endpoints	X			PK endpoints
Safety analyses	X			
Demographic/baseline endpoints	X	X		

6.5 POOLING OF CENTRES

Not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Pharmacokinetics:
For the handling of missing PK data see CTP Section 7.5.1.

Laboratory values:
For the handling of missing baseline laboratory values see CTP Section 7.5.

Partial or missing dates:
For the following dates the rule described below applies: Last date patient known to be alive, drug discontinuation dates, start and end dates of concomitant therapies, start and end dates of docetaxel pre-medication, start and end dates of subsequent anti-cancer therapies, date of first histological diagnosis, and death date.

In general, all reasonable effort should be undertaken during the study to obtain these dates completely. If despite all efforts, the complete date cannot be provided but only the month and

the year, then the 15th of the month will be imputed. If only the year is reported, July 1st will be imputed. However, the imported date should never be later than the death date.

Adverse Events:
Missing or incomplete AE dates are imputed according to BI standards (3). The imputation algorithm is based on a worst case approach, i.e. the imputed AE dates will:

1. maximise the possibility for AE to be counted as treatment emergent AE
2. result in 'longest' duration of treatment emergent AEs
3. result in 'shortest' duration of non-treatment emergent AEs

Missing docetaxel infusion time:
If the time of infusion is missing, then start time of the infusion will be imputed as "0:00" and the stop time will be imputed as "1:00".

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the flowchart of the CTP.

Unless otherwise specified, baseline is defined as the latest time point before the very first administration of any study medication. If this criterion is not fulfilled, then no baseline will be derived. Note that for some trial procedures (for example Eastern Co-operative Oncology Group (ECOG) performance score, body weight, vital signs, laboratory tests) this may be the value measured on the same day when trial medication was started. In these cases it will be assumed that the measurements were taken prior to the intake of any study medication.

For nominal time points and windows of tumour imaging, see Table 7.6: 2.

Laboratory values:

Baseline is defined as the latest time point before the very first administration of any study medication. For laboratories where not only the examination date but also time are recorded, a laboratory value on the same date as first study drug administration is considered as baseline value if and only if the time of laboratory value is before or at the same time as the time of first study drug administration. If any of those times are missing and the date of laboratory value is equal to the date of first study drug administration, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow the guideline “Reporting of Clinical Trials and Project Summaries” (4).

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard deviation (StD)/ Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to Mean, StD, Min and Max.

For time-to-event analysis tables, the set of statistics is: number of patients [N(%)], Number of patients with event [N(%)],Number of patients censored [N(%)], <Time to event> [months] followed by P25 (25^{th} percentile), median, P75 (75^{th} percentile). If not specified otherwise, the duration as well as the time to event will be displayed in months and a final decision will be made at the last RPM.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

The denominator of the main categories is defined by the number of patients in the used patient set. The main categories define the denominators of the subcategories. Subcategories should be intended and "[N(%)]" to be displayed only for the main category.

If a table includes only categorical data, "N[(%)]" is to be displayed in the column header only.

Abbreviations (e.g. Wors.) should not be displayed without any explanations. They will be either spelled out in the table or explained in footnotes (whatever is more reasonable from the programming point of view).

If applicable, conversion from days to weeks, months and years will be as follows:

- Weeks = Days/7
- Months = (Days ×12)/365.25
- Years = Days/365.25.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Standard descriptive analyses and summary tables are planned for this section of the report. Data will be summarised by dose cohort and a “total” column will be included in the summary tables.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.
Concomitant diseases will be coded similarly as AEs based on the most current Medical Dictionary for Regulatory Activities (MedDRA) version.

Concomitant therapies (CTs) will be coded according to the World Health Organisation Drug Dictionary (WHO DD). CTs will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorise CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level-three category will be counted more than once; footnotes will clarify this possible double counting in tables.

The CTR will contain tables for previous and concomitant therapies started at baseline including CTs stopped prior to the first intake of study medication as well as CTs started before the first intake of study medication and continued during study drug treatment and separately CTs that were initiated after the start of study medication.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report.

7.4 PRIMARY ENDPOINTS

The primary endpoints of this trial are the MTD and the number of patients with DLTs during the first treatment cycle. The MTD is determined from the occurrences of DLTs during the first treatment cycle. The primary analysis is for the determination of the MTD. The purpose of this analysis is to summarize and document the data that led to the selection of the MTD. Therefore, an overall summary of patients with DLTs (see CTP Section 5.3.6 for the definition of DLTs) which occurred during the first treatment cycle will be provided for each dose cohort. Patients, if any, who did not complete the first treatment cycle for reasons other than DLT will be excluded from the analysis of the primary endpoint.

A summary of the number of patients with DLTs overall in the on-treatment period will be also given by initial treatment and displayed in a similar format to the summary of DLTs occurring in the first treatment cycle.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Other Secondary endpoints

This section is not applicable as no secondary endpoint has been specified in the protocol.

7.7 EXTENT OF EXPOSURE

The duration of drug intake and the estimated dose intensity will be summarised descriptively.

The frequency of patients with dose reductions as well as the time to first dose reduction will be described for nintedanib.

7.8 SAFETY ANALYSIS

All safety analyses besides the determination of the MTD will be performed on the TS. The determination of the MTD will be based on the MTD evaluation set. Patients who were replaced within the first treatment cycle will be excluded from the MTD evaluation set but will be considered for all other safety evaluations based on the treated set. Replaced patients will be listed.

7.8.1 Adverse events

The analyses of adverse events will be descriptive in nature and will be based on BI standards. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. AEs will be coded with the most recent version of MedDRA. The severity of AEs will be scaled according to common terminology criteria for adverse events (CTCAE) version 4.03 (5) According to the BI standards, multiple recordings of adverse events will be

collapsed to episodes on the MedDRA lowest level term and multiple episodes will be condensed to records on the preferred term and SOC level. Please refer to 001-MCG-156 version 5.0 (6) for detailed explanations of the collapsing and condensing procedures applied in AE data handling and analyses.

CTCAE grade will be an additional criterion for collapsing and condensing AEs. The worst (maximum) CTCAE grade will be assigned to episodes and records. CTCAE grade will be displayed in AE listings.

The analysis of adverse events will be based on the concept of treatment emergent adverse events, where a treatment emergent AE has an onset in the analysing treatment period. The main AE analysis using the treated set will be based on the "on-treatment period". AEs with onset date in the screening-period or post-treatment-period will listed separately. That means that all AEs occurring between first drug intake till 28 days after last drug intake will be assigned to the allocated treatment. All AEs occurring before first drug intake will be assigned to 'screening' and all adverse events occurring after last drug intake + 28 days will be assigned to 'post-treatment' (for listings only). For details on the treatment definition, see Section 6.1.

Adverse events will be displayed by the initial assigned dose of nintedanib and docetaxel administered on the first day of treatment with study medication in the summary tables. In addition, a listing will be provided, detailing the actual dose of nintedanib and docetaxel administered on the day when the AE starts. Patients with treatment information missing will not be displayed in the safety tables. A separate listing will be provided for these patients.

Adverse events will be reported with start day and end day calculated relative to the first day of treatment with study medication. The system organ classes (SOCs) will be sorted alphabetically. Preferred terms (PTs) will be sorted by descending frequency of adverse events (within SOC) in the "total" group.

An analysis of DLTs during the first treatment cycle for patients from the MTD evaluation set will be displayed. This analysis will reflect the dose escalation and MTD determination. In addition, analyses showing DLTs during the on-treatment period for all patients from the treated set will be done to further characterise the MTD and determine a recommended phase II dose.

Listings of adverse events will be displayed by patients and also by medical PT.

Reporting of CTCAE grades in tables: AEs with a given CTCAE definition will be displayed in tables showing AEs by worst CTCAE grade. The preferred option for displaying the CTCAE grading within AE tables (Section 15) should be "All Grades", "Grade 1/2" and "Grade 3/4/5". AEs with missing CTCAE or CTCAE grades not equal to 1 to 5 will be displayed under the category "All Grades", but no category "Missing Grade" should be displayed and therefore the categories "Grade 1/2" and "Grade 3/4/5" might not add up to the category "All Grades".

A separate table will show AEs leading to death. In this table no CTCAE grades will be shown. For fatal AEs without CTCAE grade 5 or missing grade, the grade will be imputed as CTCAE grade 5. In the appendix (section 16.1.9.2), the categorization "All grades", "Missing

Grade", "Grade 1", "Grade 2"; "Grade 3", "Grade 4" and "Grade 5" should be used, but the "Missing Grade" column should only be displayed in case AEs with a missing CTCAE grade occurred.

An overall summary of adverse events will be presented.

Incidence and severity of adverse events
The incidence of AEs overall (irrespective of relatedness to study medication), related AEs, and of serious AEs (SAE) will be reported by severity according to CTCAE grades.

Other significant adverse events
Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction or permanent discontinuation of study medication (nintedanib or docetaxel, dose reductions only allowed for nintedanib per CTP). The incidence of

- AEs leading to dose reduction of nintedanib
- AEs leading to overall permanent discontinuation of last study medication
- AEs leading to discontinuation of nintedanib or docetaxel
- AEs leading to discontinuation of nintedanib and docetaxel
- AEs leading to discontinuation of nintedanib
- AEs leading to discontinuation of docetaxel

will be reported by severity according to CTCAE grades.
A listing of patients who developed 'other significant' AEs will be provided and a flag for serious and non-serious will be included.

Adverse events of special interest
AESIs as defined in the CTP and collected in the eCRF will be analysed descriptively.
Deaths and fatal AEs
AEs leading to death during the on-treatment period will be tabulated. Reported fatal AEs that occurred in the post-study phase will be listed.

Adverse Events by UDAEC
User defined adverse event categories (UDAECs) as defined on project level will be derived and the latest version will be used for analysis. AEs by UDAECs will be displayed as follows:

1. AEs by UDAEC tables presenting the UDAECs only: UDAECs sorted by frequency of UDAEC.

2. AEs by UDAEC tables presenting the UDAECs and preferred terms: The UDAECs will be sorted alphabetically. Preferred terms will be sorted by descending frequency of adverse events (within UDAEC),

3. A listing of the used coding of the UDAECs will be provided in Appendix 16.2 of the CTR.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (see "Display and Analysis of Laboratory Data", 7). The analysis of laboratory data will use the same "analysing treatments" as described for the AEs, except for that the baseline laboratory value will be included in the "on-treatment period". Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses.

Descriptive statistics, including change from baseline and frequency of patients with transitions relative to the reference range, will be provided. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE v4.03. The following outputs will be presented:

- Worst CTCAE grade experienced during the on-treatment phase.

- Transitions of CTCAE grade from baseline to worst laboratory value, from worst to last laboratory value on treatment, and from baseline to last laboratory value during the on-treatment phase.

Worst laboratory value and its CTCAE grade (highest CTCAE grade) over all courses will be calculated for each laboratory parameter specified in CTP Section 5.3.3.

Patients with missing CTCAE grade at baseline or no baseline value but post baseline values will be displayed in the category "Missing CTCAE grade at baseline".
Generally, in case only one direction of worsening (high or low laboratory values) is specified in the CTCAE document, there is no need to examine the other direction. Therefore for calculating the change in CTCAE grade from baseline / pre-dose level, patients with a CTCAE Grade of "-9" (no CTCAE grade defined) will be treated as a CTCAE Grade 0 for all analyses. In laboratory listings, the CTCAE grade will be displayed as "-9".

For Uric Acid and Hypokalemia, the CTCAE grade cannot always be assigned by the laboratory parameter itself as two different CTCAE grades have the same laboratory constellation, but are distinguished by additional clinical parameter. In this case a CTCAE grade of "-1" will be assigned initially. Patients with a CTCAE Grade of "-1" will be treated as

- Grade 1 for Uric Acid
- Grade 1 for Hypokalemia

for all analyses. In laboratory listings, the CTCAE grade will be displayed as "-1".

Possible clinically significant abnormal laboratory values are defined as those laboratory values that are of CTCAE Grade ≥ 2 and show an increase from baseline value by at least one CTCAE grade. For those parameters for which no CTCAE has been defined, BI standard definition will be used to determine possible clinical significance. Frequency of patients with possible clinically significant abnormal laboratory values will be provided whenever applicable. If no baseline value is available but the patient has a post-baseline laboratory value of CTCAE Grade ≥ 2 an increase from baseline will be assumed, i.e. the laboratory value considered as possible clinically significant.

Hepatic enzyme elevations (potential Hy's law cases):
Patients fulfilling the criteria for potential Hy's law cases will be tabulated. These are defined as those cases where a combination of all the following events occurs: any on-treatment value of AST or ALT (or both) is > 3x ULN with total bilirubin ≥ 2x ULN and ALP < 2x ULN. The events can occur in any order, but must occur within 14 days from the previous event, i.e. the second event must occur within 14 days from the first event and the third event must occur within 14 days from the second event, etc.
In addition, a separate listing will be given showing patients with missing parameters in the above given time frames.

7.8.3 Vital signs

Descriptive statistics are planned for this section of the report.

7.8.4 ECG

Newly emergent abnormalities will be recorded and analysed as AEs.

7.8.5 Others

Other parameters relevant for safety as height, weight, and ECOG score will be analysed descriptively and displayed in patient listings.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**26-AUG-16**		None	This is the initial TSAP with necessary information for trial conduct.
Final	**21-FEB-17**		1 - 10	This is the final TSAP